REMARKS

Claims 1-6 were pending in the present application. Claims 1 and 2 have been amended to recite, *inter alia*, a "test small organic molecule" instead of a "test compound". Support for this amendment can be found in the specification at page 24, line 6. Claims 2 has been amended to recite, *inter alia*, a radiolabeled N-acetylglucoseamine phosphate acceptor or radiolabeled glucose. Support for this amendment can be found in the specification at page 18, lines 16-17. Claims 2-4 have been amended to recite, *inter alia*, a radiolabeled terminal phosphate acceptor and correct antecedent basis. Support for this amendment can be found in the specification at page 18, lines 16-17. Claims 1 and 2 has also been amended to correct a grammatical error.

None of the above-made amendments introduces new matter. Applicants respectfully request entry of the amendments made herein. Upon entry of the amendments herein, Claims 1-6 will be pending and under consideration.

Claims Rejections - 35 U.S.C. § 112, second paragraph

Claims 1, 2 and claims depending thereupon have been rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner alleges that Claims 1 and 2 lack internal antecedent basis for addressing a "specific small organic compound" and "a test compound". For clarity purposes only, Applicants have amended Claims 1 and 2 to refer to a "test small organic molecule". Accordingly, this rejection has been obviated and Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that, with respect to Claims 1-6, the term "small organic molecule" is vague and indefinite. The Examiner alleges that the specification does not provide a standard for ascertaining what constitutes a "small organic molecule", and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Applicants respectfully disagree.

> The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
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> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.
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> In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph. *See, e.g., Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). *See* also *In re Larsen*, No. 01-1092 (Fed. Cir. May 9, 2001). *See* MPEP § 2173.02
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> Applicants submit that the term "small organic molecule" is definite in light of the

application disclosure and the teachings of the prior art, and is a term of art well known to one possessing the ordinary skill in the pertinent art at the time the invention was made.

The application disclosure teaches use of a small organic molecule library available from Discovery Technology Ltd. which consists of molecules from commercial sources such as Specs and Comgenex. *See* the specification at page 24, lines 6-8. Furthermore, three representative compounds are provided in Table III. *See* the specification at page 25, line 19 to page 26, line 5.

The teachings of the prior art provide numerous examples of the use of the term "small organic molecule". For example, libraries of small organic molecules are described in U.S. Patent No. 6,207,391 including, "*e.g.*, benzodiazepines, Baum C&EN, January 18, page 33 (1993); isoprenoids, U.S. Pat. No. 5,569,588; thiazolidinones and metathiazanones, U.S. Pat. No. 5,549,974; pyrrolidines, U.S. Pat. Nos. 5,525,735 and 5,519,134; morpholino compounds, U.S. Pat. No. 5,506,337; benzodiazepines, U.S. Pat. No. 5,288,514, and the like". U.S. Patent No. 6,048,698 provides non-limiting examples of small organic molecules such as alkenes, alkynes, alcohols, aldehydes, ketones, esters, carboxylic acids, aromatic carbocycles, heterocycles, dienes, thiols, sulfides, disulfides, epoxides, ethers, amines, imines, phosphates, amides, thioethers, sulfonates and halogenated compounds. In addition, other U.S. Patents contain claim language directed to small organic molecules but fail to define the term in the specification, strongly suggesting that the term "small organic molecule" is a term understood by one of ordinary skill in the art. *See, e.g.*, U.S. Patent Nos. 6,051,373 and 6,132,978.

Small organic molecules are taught in the prior art to form the basis for most traditional drugs and are contrasted with a macromolecular approach which includes recombinant peptides, monoclonal antibodies and oligonucleotide/gene fragment approaches. *See* Cho *et al.*, 1996, Trends Biotechnol 14:153-8. In the context of small molecule libraries, numerous reviews and publications discuss the synthesis of libraries of small organic molecules. *See, e.g.*, Thompson *et al.*, 1996, Chem Rev 96:555-600.

Furthermore, one of ordinary skill in the art would interpret the claims of the present invention by imparting a specific meaning to the term "small organic molecule". In light of the specification, one of skill in the art would understand "small organic molecule" to mean a carbon containing molecule of a size comparable to known therapeutic agents, especially, antimicrobial agents. Further, given the disclosure, one of ordinary skill in the art would recognize that other small organic molecule libraries can be used.

In light of these factors, Applicants submit that the claims set out and circumscribe the particular subject matter with a reasonable degree of clarity and particularity. The claimed methods are directed to screening methods comprising specific steps. One of ordinary skill in the art, examining the claim as a whole, would recognize that the steps of the method are critical to the scope of the claim and that the methods steps provide notice to those of skill in the art. The steps of the claimed methods themselves are generally applicable to testing various compounds, including small organic molecules, for antimicrobial activity. Thus, Claims 1-6 apprise one of ordinary skill in the art

of their scope and, therefore, serve the notice function required by 35 U.S.C. 112, second paragraph. Accordingly, Applicants respectfully request withdrawal of this rejection.

The Examiner further alleges that, with respect to Claim 2, that it is not clear whether the term "radiolabeled" refers to N-acetylglucoseamine alone or to both N-acetylglucoseamine and glucose and whether the terminal phosphate acceptor is radiolabeled. For clarity purposes only, Applicants have amended Claim 2 to refer to a radiolabeled N-acetylglucoseamine phosphate acceptor or radiolabeled glucose. Further, Applicants have amended Claims 2-4 to recite, *inter alia*, a radiolabeled terminal phosphate acceptor. Accordingly, this rejection has been obviated and Applicants respectfully request withdrawal of this rejection.

Double Patenting

Claims 1-6 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-8 of U.S. Patent No. 6,245,502 ("'502 patent"). The Examiner asserted that Claims 1-6 of the instant application and Claims 1-8 of the '502 patent are drawn to a screening assay for inhibitors of enzyme 1. The Examiner further asserts that the scope of the claims overlap in that the claims of the instant application are directed to "small organic molecules" while the claims of the '502 patent are directed to peptides.

In response, while not admitting that the claims of the above-identified patent application are not patentably distinct from claim 1-8 of U.S. Patent No. 6,245,502, Applicants, upon indication of allowable subject matter, will submit a Terminal Disclaimer under 37 C.F.R. § 1.321(c) of the above-identified application.

Claim Rejections - 35 U.S.C. § 103

Claims 1-6 were rejected under 35 U.S.C. 103(a) as allegedly being obvious over Saier *et al.*, 1980, J Biol Chem 255:8579-84 ("Saier") or Chauvin *et al.*, 1996, Research in Microbiology 147:471-9 ("Chauvin") and Powell *et al.*, 1995, J Biol Chem 270:4822-39 ("Powell") in view of U.S. Patent 5,698,428 ("Abo") or U.S. Patent 5,700,675 ("Rubin"). Applicants respectfully disagree.

The Examiner states that Powell teaches that the bacterial phosphotransferase system consists of several phosphoryl transfer proteins, including enzyme I, and mediates the uptake and concomitant phosphorylation of many carbohydrates. The Examiner states that Saier or Chauvin teach that enzyme I is an essential first step of the phosphotransferase system.

The Examiner states that Abo or Rubin teach screening assays for inhibitors of phosphorylation reactions.

The Examiner thus concludes that it would have been *prima facie* obvious to one skilled in the art, in view of the importance of enzyme I in bacterial cell growth, to search for antimicrobial agents which impair enzyme I. The Examiner asserts that the motivation to apply known assay methods to find agents with inhibit phosphotransferase comes from obtaining compounds with a desired pharmacological effect. Applicants respectfully disagree for the reasons

below.

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).
>
> To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

The present invention relates to screening assays to identify specific small organic molecules which acts as antimicrobials by inhibiting or uncoupling enzyme I. In one embodiment, a test small organic molecule is added to a reaction mixture containing enzyme I and phosphoenolpyruvate and measuring pyruvate in the presence of lactate dehydrogenase and NADH. In another embodiment, a test small organic molecule is added to a reaction mixture containing enzyme I, phosphoenolpyruvate and a radiolabeled N-acetylglucoseamine phosphate acceptor or radiolabeled glucose and isolating the radiolabeled terminal phosphate acceptor to measure its level of phosphorylation.

The cited prior art does not provide a suggestion or motivation for the present invention. Saier and Chauvin teach the steps involved in PTS reactions and Chauvin teaches that Enzyme I is the first enzyme in the phosphotransfer sequence and a potential regulator of the bacterial phosphoenolpyruvate : glycose PTS. Powell teaches that PTS "mediates the uptake and concomitant phosphorylation of many carbohydrates and consists of several phosphoryl transfer proteins". Contrary to what the Examiner asserts, none of these references teaches or suggests that enzyme I is essential for the survival of bacteria and that its inhibition would compromise cell growth, *i.e.*, would be an appropriate or successful target for an antimicrobial agent. While Enzyme I has been described in the prior art, it has <u>not</u> been identified in the prior art as a target for identifying antibacterial agents, rather, Enzyme I as a target for an antimicrobial agent is taught in the instant application. In addition, according to the inventors of the present invention, the fact that a functioning enzyme I is not essential for bacterial growth on an undefined (rich) media in the laboratory, makes enzyme I *prima facie* appear unlikely to be a target of antimicrobial agents (such a statement can be provided in a declaration by the inventors if requested by the Examiner). Thus, there is <u>no suggestion</u> in Saier, Chauvin, or Powell that an agent which acts to inhibit or uncouple the PTS would act effectively as an antimicrobial agent.

Furthermore, the deficiencies of Saier, Chauvin and Powell are not remedied by a combination with Abo or Rubin. There is simply no motivation to combine Saier or Chauvin and Powell with Abo or Rubin. Abo and Rubin describe human serine kinases which are targets for the identification of novel anti-cancer agents, which is completely unrelated to the bacterial PTS. The

eukaryotic serine kinases function in a different way from bacterial serine kinases. Unlike the eukaryotic serine kinases, the bacterial PTS functions not only as an intracellular signaling system but also as an intracellular energy-transducing system. Eukaryotes do not have any system which is comparable to the bacterial PTS system. In particular, Enzyme I is very different from any known enzyme. Thus, the screening methods of Abo and Rubin which identify inhibitors of eukaryotic serine kinases, would not be applicable to the bacterial PTS. The proteins of the prokaryotic PTS and in particular Enzyme I are phosphorylated at histidine residues. The phosphohistidine bond is very different from the phosphoserine bond of eukaryotic kinases. The phosphohistidine bond is very labile and of transient nature, whereas the phosphoserine bond is indefinitely stable, unless it is hydrolysed by a specific phosphoserine phosphatase. Further, phosphohistidines are not a substrate for serine phosphatases, nor do phosphohistidines play a role in mammalian signaling system. The molecular mechanisms of serine phosphorylation and histidine phosphorylation are very different. The former requires ATP or GTP as phosphoryldonor and follow bi bi reaction kinetics whereas the latter utilizes phosphoenolpyruvate as phosphoryl donor and follows ping pong kinetics with a phospho-protein (phospho-His) intermediate. An inhibitor which specifically prevents the phosphoryltransfer between Enzyme I and Hpr is unlikely to act upon eukaryotic serine kinases. If it did so, it would be highly toxic and therefore, inappropriate as an antiinfective for the protection of humans and animals against infective diseases. Thus, given the basic differences in enzymatic activity between the prokaryotic and eukaryotic serine kinase cascades there would be no motivation to combine Saier or Chauvin and Powell with Abo or Rubin. Furthermore, there is simply no eukaryotic counterpart to Enzyme I, thus, there cannot possibly be any motivation to combine Saier or Chauvin and Powell, which describes procaryotes, with Abo or Rubin, which are directed to inhibitors of eukaryotic serine kinases.

Thus, one skilled in the art would not be motivated to apply the various screening assays for inhibitors of serine kinase-dependent phosphorylation reactions, as described in Abo and Rubin, to a prokaryotic system. The difference in structure of the peptides and the chemistry of the phosphorylated amino acids and the different chemical reaction mechanisms between the eukaryotic and prokaryotic systems all indicate that the art cited does not render the present invention obvious.

Furthermore, Saier or Chauvin and Powell, whether alone or in combination with Abo or Rubin, do not provide a reasonable expectation of success. As discussed above, none of the cited references teaches or suggests that enzyme I is essential to the survival of bacteria. Prior to the present invention, it would have been entirely unpredictable whether an inhibitor or uncoupler of Enzyme I would be an effective antimicrobial agent. Thus, the claimed screening assay for a small organic molecule antimicrobial which inhibits or uncouples enzyme I would not have had a reasonable expectation of success based on the teachings of the prior art.

Moreover, Saier or Chauvin and Powell, whether alone or in combination with Abo or Rubin, do not teach or suggest all of the claim limitations. Claim 2 is directed to, *inter alia*, adding a test small organic molecule to a reaction mixture containing enzyme I and phosphoenolpyruvate and

measuring pyruvate in the presence of lactate dehydrogenase and NADH. Claim 3 is directed to, *inter alia*, adding a test small organic molecule to a reaction mixture containing enzyme I, phosphoenolpyruvate and a radiolabeled N-acetylglucoseamine phosphate acceptor or radiolabeled glucose and isolating the radiolabeled terminal phosphate acceptor to measure its level of phosphorylation. As the Examiner states, Saier or Chauvin and Powell do not teach any particular screening assay. These references are also silent on the use of lactate dehyrogenase and NADH. Further, neither Abo nor Rubin discuss screening assays involving lactate dehyrogenase and NADH nor a radiolabeled terminal phosphate acceptor. Abo and Rubin do discuss kinase assays involving radiolabeled GTP or radiolabeled ATP, respectively, as a radiolabeled phosphate donor, not a radiolabeled phosphate acceptor. See Abo, col. 42, lines 5-33 (example 9) and Rubin, col. 19, line 24 to col. 20, line 47. In the prior art, the substrate is not radiolabeled prior to its phosphorylation. In contrast, in the assays of the present invention, radiolabeled substrate is a component of the reaction mixture. Thus, Abo and Rubin can not possibly teach or suggest radiolabeled radiolabeled N-acetylglucosamine phosphate acceptor or radiolabeled glucose. Thus, the cited references do not teach or suggest all of the claim limitations.

For the above reasons, the Examiner has not established a case of *prima facie* obviousness and the rejection should be withdrawn.

CONCLUSION

Applicants respectfully request that the amendment and remarks made herein be entered and made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

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James G. Markey 31,636
(Reg. No.)

PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090